1877-78

White



# Inaugural Dissertation

for

— M.D. Degree —

by.

James Walls White.

# On
# Salicylic Acid

# — On —
# — Salicylic Acid —

Of all the new remedies that have found a place in modern Materia Medica, there are perhaps few that will receive more lasting appreciation than Salicylic Acid & its compounds; and at the present time when the theory of Bacteria and Micrococci has attained to such a prominent place in connection with Zymotic & inflammatory diseases, all substances that lay any claims to powers of destroying these Microzymes cannot fail to be of interest.

Salicine is one of those old Medicines of difinite and well known properties, that never attained to

any prominent place in the class of remedies to which it belongs, until the triumphs of modern Chemistry, penetrating more deeply into the secrets of nature, have shown its close relation to other substances of known Antiseptic powers.

Salicine was discovered by Buchner in 1828 in the bark of the Willow. He isolated it by treating a strong decoction with Lime & Alcohol, to remove the Tannin, gummy & mucilaginous matters, filtering off the clear liquor, evaporating it to crystallization, & purifying the crystals by means of Animal Charcoal; when he obtained it in the form of minute rectangular plates. Its taste is somewhat bitter & aromatic, it is soluble in water & alcohol, but insoluble in Aether, and gives with Sulphuric Acid a brilliant red colour. (16 oz of Willow Bark yielding 5 drams or about ½ p.c. of Salicine.)

It is now prepared by treating the bark of the Willow and allied species with boiling water. concentrating the infusions. digesting the liquor with Lead Oxide, filtering and passing through it a current of Sulphuretted Hydrogen gas. to remove the excess of Lead. evaporating to crystallization. purifying by animal charcoal and recrystallizing. when it is obtained in the form of silky needles.

$C_{12} H_{18} O_7$.

When Salicine is distilled with a mixture of Bichromate of potash and Sulphuric Acid. there is obtained among other products. a yellow sweet-scented Oil. Salicylol ($C_7 H_6 O_2$) identical in all respects with the Volatile Oil yielded by the flowers of the Spirea Ulmaria

When Salicylol or Salicine is fused with potassium Hydrate. Salicylate of potash is produced.

$$C_7 H_6 O_2 + KHO = C_7 H_5 O_3 K + H \Rightarrow$$

By acting on the Salicylate of potash thus formed, by Hydrochloric Acid, the Salicylic Acid is set free.— In the Oil of Wintergreen, in the bark of the Sweet-Birch and other plants, this substance exists in the form of Salicylic Methyl. To obtain the Salicylic Acid from these, say the Oil of Wintergreen, it is heated with the Caustic Potash, which unites with the acid as a salicylic of Potash, which is separated, and then decomposed by Hydrochloric Acid setting the acid free as in the case of the Salicine,

And what is more interesting, is, that by distilling a mixture of Salicylic Acid, Wood Spirits and Sulphuric Acid at a temperature of 280° C, a Salicylate of Methyl is obtained, that has an odour almost identical with that of the natural Oil of Wintergreen. And when Salicylic Acid and Carbonate of Potash is mixed and exposed to the air, it becomes yellow, and yields on distillation

a perfume having the Odour of Ottar of Roses.

So long as Salicylic Acid was only to be obtained from these organic Substances, the Supply being limited, and the price high, it was only to be obtained by the few and experimented with as a Medical Curiosity, And it was not until the discovery by Professor Kolbe of Leipzig that it could be prepared in unlimited quantity and at a moderate price, by the action of certain reagents on Carbolic Acid, that it has come within the reach of the general Profession, and its Medicinal properties have been more fully experimented on.

Kolbe prepared it, by acting on Carbolic Acid with a Solution of Caustic Soda in equivalent proportions heating the mixture to a temperature of 220° to 250° C. evaporating to dryness, and passing over the Salt so obtained a current of dry Carbonic Anhydrate

till Carbolic Acid ceased to be given off. (the Salt being a dicarbolate) The Sodium Salicylate so obtained is solved in water and treated with Hydrochloric Acid which separates the Salicylic Acid as a brown crystaline Mass. This is heated in a retort to 170°C. and a current of superheated steam passed into it, when the acid distills over and is obtained as pure white crystals.

But if potash be substituted for the Soda in this reaction, the resulting Acid is not a Salicylic but Paroxybenzoic, which possesses no disinfectant properties whatever. If on the other hand Cresol be substituted for phenol, Cresotic Acid is obtained which like Salicylic Acid is disinfectant; but whither it can be administered internally with the same freedom as Salicylic is a matter that has yet to be investigated.

By this formula of Kolbe's it is that most of the Salicylic Acid of commerce is at present Prepared, and it may account for how from careless manipulation it may become contaminated with Carbolic or Cresotic Acids, and the presence of these may have much to do with the many diverse opinions that have been formed of its physiological actions, as has been noted by the different observers, and so given rise to the many conflicting opinions that are entertained regarding it.

This Acid was also obtained by Gerland from Anthranilic Acid, (a product of the oxidation of Indigo) by the action of Nitrous Acid on it - a fact chemically interesting as illustrative of the great plastic powers of Organic compounds - and the close affinity that may exist between

Substances widely separated in appearance + physical properties.

The Chemistry of this substance is also peculiarly interesting, from the close relationship that exists between it and other substances of known Antiseptic Powers; Carbolic Acid on the one hand and Benzoic Acid on the other, with Gallic Acid not far removed; and the fact that all these give decided colours with Ferric Salts, points them all to a common origin, or at least, as closely related to the widely distributed Tannic Acid with its well know astringent and Antiseptic properties.-

Carbolic Acid $C_6 H_6 O$

Benzoic Acid $C_7 H_6 O_2$

Salicylic Acid $C_7 H_6 O_3$

Gallic Acid $C_7 H_6 O_5$ -

And particularly the knowledge that Salicylic

Acid can be formed from Carbolic & Carbonic Acids, and that by heat it is resolved into these same substances again, pointed to its use as a preserving agent.

Pure Salicylic Acid is a white flaky crystalline powder, without smell, having a bitter somewhat acrid taste, and giving a decided acid reaction with Litmus; it is soluble in hot water, sparingly so in cold water, One part of the Acid requiring 300 of water for its solution, It is soluble in Oils, one ounce of Almond Oil taking up ten grains of it. Many substances have been proposed for increasing its solubility in water, as Sodium phosphate, Ammonium citrate &c.

Glycerine takes up about ten grains to the ounce but the addition of water reprecipitates the Acid. The most concentrated solution that has as yet been proposed, is a mixture containing

Salicylic Acid gr XXV

Boray gr VI

Glycerine ℥I ℈ —

the acid remaining in solution when it is diluted. That, for Medicinal purposes, or internal administration it should be pure, is a matter of the first importance. The test for its purity that Professor Kolbe recommends, is to solve half a gramme of the acid in ten parts of Alcohol, and to allow a little of the solution to evaporate on a watch glass, when if pure a ring of white efflorescent crystals will form around the edges; if these have a yellow colour, and particularly if they are brown the Sample is to be rejected —.

When heated it is resolved into Carbolic & Carbonic Acids $C_7 H_6 O_3 = C_6 H_6 O + CO_2$ —.

It dissolves in Sulphuric Acid without colour —

Added to a solution of potash permanganate it de-colourises it with the precipitation of the brown hydrated oxide of Manganese, but Carbolic Acid gives a similar reaction. But perhaps the most delicate test is by the addition of a solution of Ferrocyanide of Potassium to any mixture containing it, when on heating the test tube, Hydrocyanic Acid is evolved, the characteristic smell of which is at once felt; and by covering the mouth of the tube with a piece of bibulous paper moistened with a solution of a ferric + ferrous salt in potash, the immistakeable Prussian Blue is at once deposited. Nitric Acid converts both it + Carbolic Acid into Picric Acid. It is so closely allied to Carbolic Acid that to differentiate chemically between them and their salts, is a matter that requires some care; for by using the stronger reagents very similar

results are obtained. The best that I have observed is the action of the Persalts of Iron for detecting the acids when they are in a free state. The addition of a few drops of say the Liquor of the perchloride of Iron to a Solution Containing Carbolic Acid gives a pale Violet-colouration. While with Salicylic Acid it gives a dark Mauve-red. For the salts of these acids the Sulpho-Carbolate of Soda & the Salicylate of Soda, a weak solution of the proto-sulphate of Iron gives the readiest reaction producing with the Salicylates a red or purplish red solution, while with the Sulpho-carbolates it gives no reaction.

Thiersch was the first to apply it as an Antiseptic in Surgery, and thinks it equal if not in many points superior to Carbolic Acid. Its Solution is colourless, non-Volatile, it does not irritate open and granulating Surfaces, nor is it absorbed by them

He used a Solution of one part of Acid in 300 parts of water for all ordinary Surgical operations, and also a Stronger Solution, of one part of acid 5 parts of Sodium Phosphate in 50 parts of water, + also a powder of one part of Acid mixed with 30 parts of powdered Starch. So far as it has been tried in this country it seems to lack many of the properties that render Carbolic Acid so valuable especially in larger Operations. Its non volatility as compared with that of Carbolic Acid is looked on as a disadvantage, from the idea that the volatile Spray of the latter not only destroys the germs on the parts operated on, but also such as may be floating in the surrounding air. Its corrosive action also on the instruments it is brought in contact with forms a serious objection to its use.

One the other hand its non-irritant properties, and

the use of it being unattended by any symptoms of constitutional disturbance arising from its being absorbed links it more closely to Boracic Acid. An ointment of Salicylic Acid has been found to be of great service in cases of Sloughing Ulcers, especially those of a cancerous origin, in removing the fœtid odour they emit and destroying the germs of putrifaction engendered in them: even when applied in powder undiluted to a granulating surface, it causes no irritation. In solution with Borax, which increases its solubility, it forms an admirable gargle in Diphtheritic & Ulcerated Sore throat: Combined with Olive Oil it is said to form an excellent remedy for Burns; and in Eczema & Skin diseases it has been highly spoken of. An Antiseptic dressing has been prepared by saturating cotton wool with a strong solution

of it, and drying it, which seems to have more decided virtues than Boracic Lint. Infact so far as experiments with this substance have gone, all point to its being a remedy of no mean power, destined yet to attain a wide range of application.

As an antiferment it has been very largely experimented with, and as such has been proved to be at least three times more powerful than Carbolic Acid; When added to organic fluids it has been found to prevent fermentation and decay, and seems to be well suited for preserving saccharine solutions prone to ferment, as the syrups of the vegetable Acids. For Lime Juice it is specially applicable, and I have found that the addition of one grain to the ounce has effectually prevented the formation of Mould or the signs of decay, in samples but loosely corked for six months

the same liquor without it becoming covered with fungi in less than a week; it however darkens the colour of the juice, but does not injure its flavour. As a substitute for Sulphurous Acid and the Sulphites at present so largely used for preserving this substance, it possesses great many advantages; the smell of the Sulphurous Acid is disagreeable & through time it becomes oxidized into Sulphuric Acid. Salicylic Acid has no smell and when taken in small quantities internally, it produces no injurious effects. For the preservation of light wines, Beers and fermented liquors it should be of value, and for preserving drinking water on board ships on long voyages it is at present being tried.

As to its physiological effects, when administered internally, Kolbe experimenting on himself, took

for some time one and a half grammes daily without feeling any inconvenience or ill effects. Much has been written and much doubt still exists as to how or when it should be administered, and I am inclined to think that much of the unsettled opinions regarding it, have arisen from the use of impure samples. From the presence, as I have already indicated of Carbolic Acid, Cresolic Acid and perhaps of other substances, the Chemistry of which has not yet been investigated, which may be formed during the process of manufacture, and - from want of proper care may remain mixed with it. And also from this curious anomaly, that the salts of Salicylic Acid possess no disinfectant properties; so that even when pure Acid was used the combination with it of alkalies or Alkaline salts to render it more soluble or otherwise, or as already

noticed. that by the addition of a potash salt the Salicylic Acid may become converted into a comparatively inert paraoxy benzoate. and hence the failure of antiseptic + antipyretic effects. As an Antipyretic in lowering the temperature and relieving the pain in Rheumatic Fever, the Acid. the Sodium Salicylate and the Salicine, are becoming more + more acknowledged as remedies of decided power, as almost to take the place of Specifics. But frequently the Salicylic Acid + the Sodium Salicylate are found when pushed in large doses to produce typhoid symptoms with vomiting and gastric derangement. while the use of Salicine itself is more to be depended on. The experience of Dr. McLagan who has experimented so largely and done so much to introduce these substances, has led him to give preference

to the Salicine. May not much of this depend on the impurities of the Acid and its compounds.

If then as Lister and others have clearly demonstrated that putrifaction and fermentation, are always associated with the presence of Bacteria & Vibriones, whither attracted thither by decaying matter, or their Sporules being ever present in the surrounding air, find in these altered states a suitable pabulum — whereon to feed, or be they generated 'de novo' as Bastian would have us believe. And also that in Zymotic and contageous fevers, the presence of these Microzymes have been clearly demonstrated as abounding in the blood & viscera of the infected.

In the Malarial Fevers, Quinine has long held its place as a specific, in arresting the destruction of blood and tissues of which the high fever is the index.

Salicine & the Salicylates have been found to arrest the same process in Rheumatism and acute febrile states, either, perhaps by rendering the fluids unsuited to these organisms, or killing them in their lair. In the Specific Fevers, the fluids in all the tissues and excreta possess a high degree of alkalinity, to correct which the mineral acids have been used with advantage.

But how to explain the fact that out of the body, the Salts of Salicylic Acid possess no antiseptic properties, and yet as antipyretics they are useful. To Professor Binz of Bonn are we indebted for the rationale of their Action. He has shown by careful experiment, that when a solution of Sodium Salicylate is shaken up with Ether, the Ether on evaporation yields no appreciable residue, but if Carbonic Acid be passed into the same solution

and agitated with it, the Salicylic Acid is partly liberated. (the Salt being most soluble in water, the Acid in the Ether,) and on now evaporating a portion of the Ether, crystals of the acid are obtained; and that by several repetitions of this process all the Salicylic Acid may be removed.

Putrescible mixtures also were found when treated with Sodium Salicylate and Carbonic Acid to resist the putrifactive changes for a much longer period than those treated by the Salicylate of Soda alone. Hence he infers that the explanation of the action of the Salicylic salts, is to be found in the fact that when they are absorbed into the blood they are brought in contact with the Carbonic Acid which is constantly generated and given off there, the Salicylic Acid is liberated from its combinations & presented to the tissues in a free state.

He also remarks "that Salicylic Acid has in some respects a near similarity to Quinine; like Quinine it cuts short the Symptoms of Malarial Poisoning, though somewhat less lastingly & surely, and it acts as a powerful antizymotic, that can be introduced into the System in large doses. It remains for a considerable time in the System, and passes out again at least partially unaltered. Of course the correspondence between the Substances as might be expected from the difference of their constitution is not complete in all respects."

Mc Lagan also holds that Salicine when given internally becomes oxidized into Salicylic Acid and is excreted as such. It thus becomes a matter of little consequence which preparation is used, seeing they are all resolved into the same substance, and all other things being equal

it will be most economical to give the pure Salicylic Acid.

The researches of Modern pathology have shown that Bacteria and Vibriones are ever present in the effete secretions of open unprotected wounds; in the Urinary Bladder when urine is decomposing; in Abscess especially pyæmic ones; in Erysipelas crowding in the outer inflammatory zones: in Diptheria they are found swarming in the lymph spaces of the Fauces & Larynx, and also in the Kidney. In Relapsing Fever, Spirala are found in abundance during the Febrile Stages. Vanishing during the intermissions; In Splenic Fever they are present in the blood and affected tissues. the Spleen is enlarged & full of them; in the Lymph of Small Pox and Vaccine Lymph they are also present; leading to the inference that these infectious Fevers owe

their contagious powers to the presence of these organisms,

The inquiries of Dr. Dougal and others, have led to assumption that there is a distinct difference between putrifaction and fermentation, at least they have shown that the former process takes place in bodies and fluids in a state of Alkalinity, and is marked by the presence of Bacteria + allied organisms, While the later is characterised by states of Acidity, accompanied by the growth of Torulae + Mycelia. They are however closely allied, the one running into the other, "Thus Acids added in small quantities to a putrid solution, putrescence is arrested and fermesence induced, Added in larger proportions to a fermenting or putrid solutions both process are arrested indefinitely, Acid Vapours render Vaccine Lymph inert:- Alkalies again added to a fresh solution, hastens

putrescence and prevents fermentation, added in larger quantities they prevent both processes; small additions to a fermenting fluid arrests fermentation + induces putrifaction." From some such basis as this it is that distinctions have been drawn between Disinfectant and Antiseptics. The former have been defined as substances that destroy the Bacteria, or do alter the fluids in which they grow as render them destructive to their substance. The latter again are such as only cause a temporary alteration in the state of matters, as stops the growth of these germs, or do alters the medium in which they exist, as prevent their further development, conserving but not destroying, merely suspending their activity.

Antipyretics again, as the name indicates, are the reducers of heat. Elevation of temperature is the constant accompaniment & characteristic sign of

Chemical reaction and chemical change.
So thus in all fevers with their high temperatures we know that there is a corresponding destruction of tissue going on; the higher the heat, the more rapid the destruction, lower the heat and you retard the waste.
In what class then we to place the Salicylic Acid? is it Disinfectant, or Antiseptic or both? Antipyretic it undoubtedly is. As we have already seen it is of greatest value in retarding waste & decay, when added to substances having an Acid reaction, it at once arrests fermentation, And on this account may we find the explanation of its decided powers in Rheumatic Fever. Where the secretions especially those of the Skin are so decidedly acid, be they Lactic Acid or not. So that when introduced into the System while in this State, its action on the Infusoria

is rapid and decided, arresting their development whither it kills them or not; it will stay their irritating effects and give nature time to extrude them. It seems also to have a direct action on the nerves of the Skin as its beneficial administration is marked by profuse sweating, which of itself in causing rapid evaporation may mechanically aid in reducing the temperature.

To prove of similar value in the Specific Fevers wherein the Secretions are marked by distinct Alkalinity, analogy would lead us to combine it with some of the stronger Mineral Acids, so as more rapidly to render the Blood slightly Acid, and then what might be called its Specific Action on the Skin or elsewhere may be made available. It has been strongly recommended as a prophylactic against the after effects of Diphtheria, for which

throat affection it forms an excellent gargle.
And it seems to me, whatever be the value of
the Bacterian theories of disease, that as a propylactic
against contageous Fevers there is an unopened
field for experimenting.
Salicylic Acid is a comparatively innocuous
substance, admitting of ready solution in the Vegetable
acids, and perhaps best of all in Lime Juice, —
of which a well preserved Syrup could be formed
and administered with ease & freedom.
We are as yet on the threshold of an inquiry,
on which the time and energies of the present
generation may be profitably expended —
And from the many workers already in the field,
on this and allied subjects, much new and
interesting information may be expected —

J. H. White